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Bicuspid Aortic valve: a frequent syndrome with a challenging outcome

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Editorial

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Abbreviations

BAov: Bicuspid Aortic valve; CHD: Congenital Heart Disease; HLHS: Hypoplastic Left Heart Syndrome; PDA: Patent Ductus Arteriosus; VSD: ventricular septal defect; CoA: Coarctation of the Aorta; CVS: cardiovascular system; AAo: Ascending Aorta; TTE: Transthoracic Echocardiography; TOE: Trans Oesophageal Echocardiography; AVR: Aortic Valve Replacement; TAVI: Transcatheter Aortic Valve Implantation.

The Bicuspid Aortic valve (BAov) has the ability not only being among the most common congenital heart diseases (CHD) but also having both a fascinating clinical presentation and a challenging outcome. It can be found in approximately 1-2% of the general population and mostly among males. When found in females it is mostly seen in severe clinical cases. This condition can present in any age from fetal to late adulthood, even...never! It has a variety of clinical spectrum that can range from the extreme form of a Hypoplastic Left Heart Syndrome (HLHS) to undetected minimal valvular disease- stenosis or/and regurgitation - or incidentally present as a sub-clinical endocarditis; only mentioning a few of its many presentations. As its adverse cardiovascular outcomes are more common than previously thought, therefore due to its high prevalence it represents a huge burden towards public cardiovascular care.

Despite Leonardo's da Vinci first description of the defect, and Sir William Osler's approach as the most common CHD, we still have more questions regarding the disease than answers¹.

Up to date, genetic causes, and clinical implications for the majority of BAov patients remain largely unknown. Possibly a genetic component exists, leading to a link to other CHD's such as Patent Ductus Arteriosus (PDA), ventricular septal defect (VSD) and coarctation of the aorta (CoA). Evidence of an autosomal dominant inheritance pattern with variable expression and incomplete penetrance in families has been described. Additionally, mutations in NOTCH1 - a mechanosensory receptor found in arteries - may associate with a BAov and valvular calcium-deposition reactivation. A familiar model involving specific mutations or distinction in GATA-5 - a transcription factor that regulates the proper embryological development of the cardiovascular system (CVS) - have been linked to specific cases of BAov and aortopathy. A multifactorial event during the embryogenesis of the semilunar valves, leads to a formation of a fusion between the aortic cusps, creating the defect, has been proposed by few researchers in the field².

Schaefer, et al. in 2008 described four subtypes of BAov: I. Fusion seen between right - left

cusps (80% cases), II. Fusion seen between right - noncoronary cusps (19% cases), III. Approximately 1% of cases with fusion between left - noncoronary cusps. (Figure 1).

An additional IV. Sub-type known as a “functional BAov”, where 3 uneven cusps can be seen with the valve closed but only two functioning, when opening, creating an echocardiographic image of a so called “fish mouth”³.

These can be identified in every day clinical assessment by 2D transthoracic echocardiography and in more detailed imaging in 3D. (Figure 2).

True BAov have only two symmetrical leaflets and two sinuses of Valsalva (Figure 2). Clinically, sub-type I is more likely to suffer stenosis in adults while subtype II valves will present pathology in younger ages (Figure 1)⁵.

Regarding the clinical presentation of a BAov we need to distinguish: A. a form pattern and B. an age pattern⁶. And although a “**silent**” form of BAov can exist and only be found as an incidental post-mortem finding the most common clinical presentation of a BAov is that of a as a **robust valvular disease**⁷.

A. Defying a form pattern; this indicates two common forms. Firstly, a **mostly stenosis** and a second **mixed form** where **regurgitation of the valve annulus** and **secondary aneurysm formations** of the AAO and augmented aortic dissection risk in nearby future can be expected.

The valve stenosis form may present from birth and/or gradually, as aging increases its amount of stenosis. In this form most probable in future the need for aortic valve replacement (AVR) is anticipated. Studies have shown this in 25-65% of patients in their late twenties age pe-

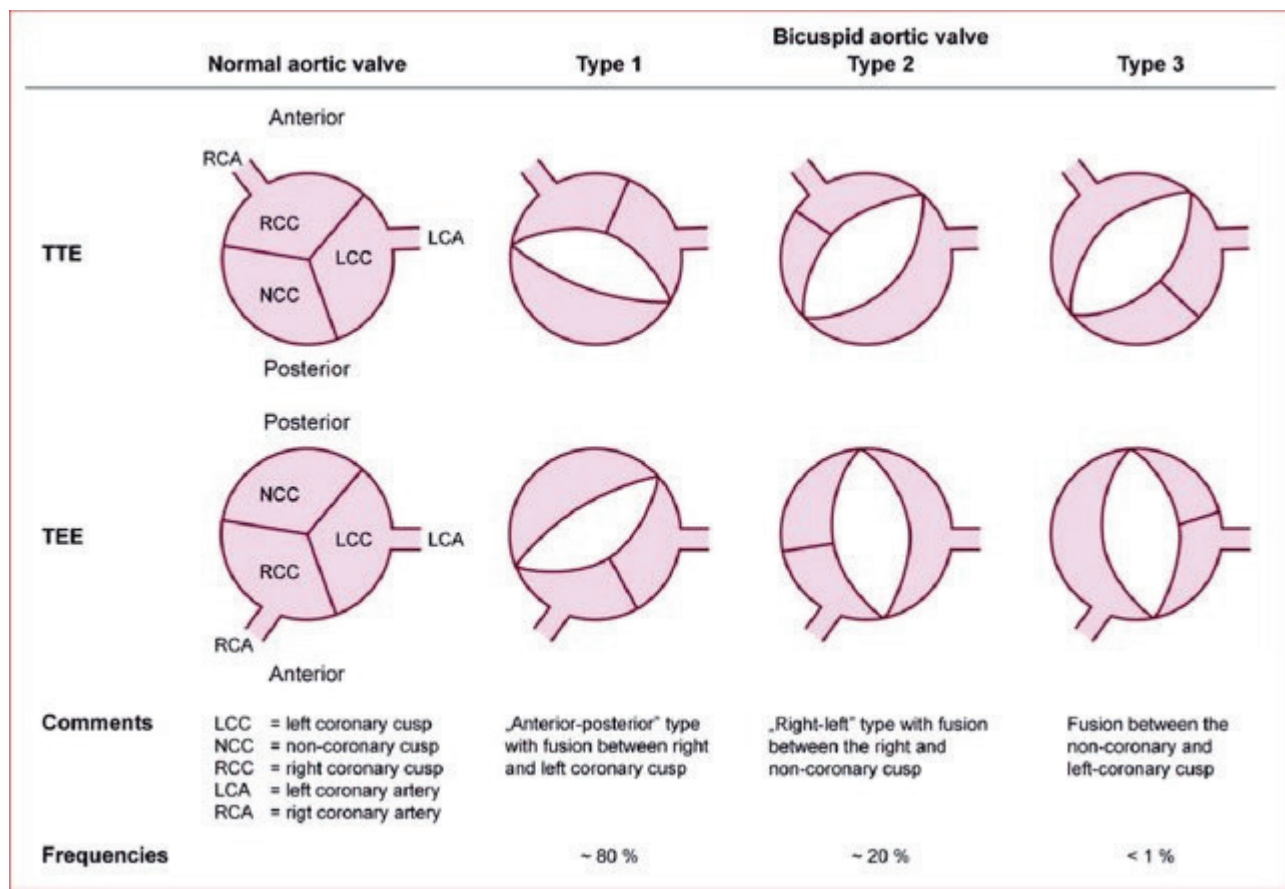


Figure 1: Anatomical classification of BAov. Courtesy of Prof. Christian R Habermann © From “Aortic aneurysms after correction of aortic coarctation: A systematic review”; February 2010; VASA.: Zeitschrift für Gefäßkrankheiten. Journal for vascular diseases 39(1):3-16

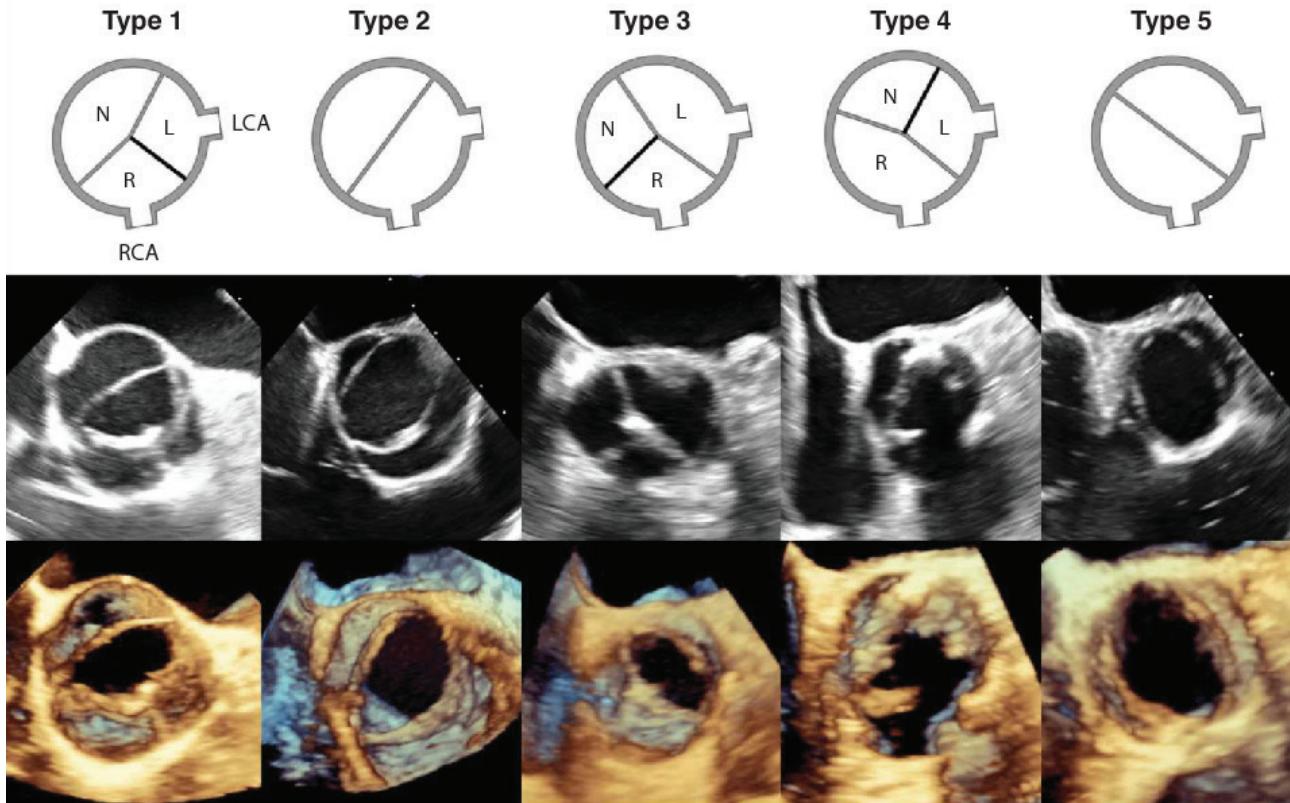


Figure 2: Courtesy of Prof. Selcen Yakar Tuluçe from his paper Assessment of bicuspid aortic valve phenotypes and associated pathologies: A transesophageal echocardiographic study. Turk Kardiyoloji Dernegi arsivi :1 December 2017

riod.

In the second form, studies have proven that 15-30% will need surgical repair of the BAovR+ between the 4th - 5th decade of their life. 45% of the group will suffer aneurysm formations while 26% will need to be operated in this age group.

Additional to the only or mostly valve clinical presentations a more **generalized aortopathy** form is also frequently seen among individuals suffering from a BAov.

Genetic evidence in combination with histological tissue alternations- because of cellular structural abnormalities including decreased fibrillin, causing smooth muscle cell detachment, and cell apoptosis. This element in collaboration to altered flow pattern abnormal jet orientation -due to uneven shear stress forces on the endothelium of the ascending aorta- because of two rather than three cusp, valve geometry, creates the setting of an aortopathy with multiple clinical

presentations. These clinical conditions involve most commonly the tubular AAO, the entire AAO, including the sinuses of Valsalva and sinotubular junction. Finally, in sub-type I BAov and male gender frequently exhibit dilatation of the area of the sinuses of Valsalva.

B. Defying the age pattern; a “**pediatric form**”, presenting earlier in life. A large study from autopsy specimens, calculated a prevalence of 6.7% of these complex CHD including a BAov as one of their elements. Examples are: BAov with: CoA (51.5%), with VSD (20.5%), with CoA and VSD, with PDA. BAov has been also reported as a part of transposition of the great arteries (1%), HLHS, complete atrioventricular canal defect, Ebstein’s anomaly, partial or total anomalous pulmonary venous drainage, tetralogy of Fallot, double-outlet right ventricle, left ventricular septal diverticulum. It can also be a part of genetic syndromes that involve CHD. Such are Turners (30%), William’s, Down’s, Marfan’s,

and Loeys-Dietz^{1,5,6}. These patients also present with a higher incidence of left dominance coronary artery pattern (57%) with higher incidence of immediate bifurcation of the left main coronary artery, and higher incidence of mean length of the left main coronary significantly shorter up to 10mm. Anomalous origins of both right and left coronary arteries and the origin of the left circumflex artery as well as a single left coronary artery, have been reported. Spontaneous coronary artery dissection may occur also. An “**adult form**”; in which: isolated stenosis (36%), regurgitation (44%), both (20%), worsening by age at least and possible by accumulation of cardiovascular risk factors that accelerate atherosclerosis, are common clinical presentations. Additional to these more “silent” clinical presentations, formation of aneurysms (17-45%), rupture of them (10%), endocarditis (0.3-2%/yearly risk) and thrombotic events have been reported^{1,6}.

The natural history of BAov has been evaluated in several studies. It is known to be variable and dependent on associated abnormalities, age of patient and anatomical subtypes.

Diagnosis is based on clinical suspicion by medical, family history or incidentally finding during a well-baby or physical examination. Late presenters are common, mostly with “isolated-adult” valvul form. The mainstay of diagnosis is echocardiography (TTE or TOE) which can provide diagnosis in most patients also detecting progression of aortopathy. Recently, the use of metalloproteinase plasma assays, computer tomography and magnetic resonance imaging, have been introduced in clinical practice diagnosis and risk stratification^{1,6}.

Decisive treatment is only by surgical means. Medicines as: b-blockers, ACE-I, ARDS, and Statins, have been used to alleviate symptoms and slow progression. The 2017 ESC and the 2020 ACC/AHA guidelines for the management of patients with valvular heart disease address all the indications, types of surgery and/or intervention strategies in adult patients. The pediatric world still suffers from a lack of guideline; although clinicians in this field are encouraged to consult on the bases of the adult above mentioned guidelines^{6,8}.

In the childhood population valve replacement is not encouraged as physical development, outgrows the prosthetic valve. Strategies to repair the stenotic or regurgitant valve or even the use of a sub-coronary Ross procedure - by an experienced surgeon- replacing the affected BAov with their own pulmonary valve and using a pulmonary homograft and the side of the extracted valve, should be used because of the excellent postoperative long-term results^{9,10}. As valve calcification in children is absent a balloon valvuloplasty procedure is possible and can be in some cases the strategy of choice. Studies have shown good follow-up in both the immediate and medium terms, follow-up. This can buy time bridging the patient before needing surgery¹¹.

For the adult population a variety of surgical approaches can address any complex clinical presentation combining surgical repair, a Ross procedure, a biological and/or mechanical valve replacement with a Bentall procedure and/or more sophisticated vascular surgical procedures such as a Tairon David or a Magdi Yacoub procedure¹². Finally, for the elderly and complicated with additional extra cardiac nosology patients, a transcatheter aortic valve replacement approach (TAVI) can be offered⁹.

In summary, there are still large gaps in understanding the pathophysiology of **BAov-associated valvopathy - aortopathy**. Today, finding of a BAov in any age patient, must be approached as a **Syndrome** and not a defined disease.

As a **take home message**, the only robust data about the **syndrome of the BAov** is that we still have many to learn in how to deal efficiently with a condition in which its high prevalence, many subtypes and clinical presentations in any age group highlights it as a **major public health issue** in the field of congenital heart disease^{1,9}.

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